Cobra-bites

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The cobra is a common snake throughout Africa and Asia, and the literature reporting experimental work with cobra venom is prodigious. In contrast, there are few clinical accounts of the effects of cobra-bites in human beings. The dogma that cobra-bites are "neurotoxic"—based on laboratory experiments in small animals—is still widespread. In fact, neurotoxic effects in human victims are rare; the main clinical feature of poisoning is local necrosis. This paper summarizes clinical observations of 47 patients bitten by the common cobra in north-west Malaysia.

Material and Methods

During 1958 to mid-1963 47 patients were selected for observation—selected as they came to Penang General Hospital or Sungei Patani Hospital, and the cobra biting the victim was personally identified as *Naja naja* (Linné) and measured in every case. Forty-five of the patients were personally observed by me, but in the two fatal cases both victims died at Sungei Patani Hospital before I could see them. Fourteen victims were bitten on Penang Island, 14 on Penang State mainland, and 19 on the adjoining central Kedah State. Methods of clinical and laboratory observation have already been outlined (Reid, Chan, and Thean, 1963; Reid, Thean, and Martin, 1963b). Local swelling, assessed by circumference measurements to the nearest 0.5 cm. at the same marked level of both feet or hands, ankles, or wrists (thinnest part), calves or forearms (fattest part), thighs or arms (middle), is expressed in cm. increase (total of all four measurement sites) compared with the unbitten limb. Poisoning is graded as: nil, negligible (local swelling but no necrosis), necrosis (local necrosis but no systemic effects), and systemic.

General Features

The features outlined in Table I reflect the occupational nature of snake-bite, which is mainly incurred by rural folk, males more commonly than females. Severity of poisoning was not significantly related to sex, age, or race. Cobras are reported to bite with more determination and effectiveness at night than in the day (Acton and Knowles, 1921). Nevertheless, most human victims are bitten in daylight—since many more are exposed to risk during the day than at night. In this series poisoning was more severe in daylight victims than in those bitten at night. Elapid snakes normally eat other snakes, but the Asian common cobra prefers rodents and therefore lives in urban as well as in rural tropical areas. Thus four of the Penang Island victims were bitten in the city of George Town and 15 were bitten near or inside their house. One of the latter (Case 23), a 10-year-old Chinese boy, found a nest of cobras in a back room, killed the mother and four of the progeny, but was bitten by the fifth, which he had overlooked. Victims bitten near the house were usually collecting firewood or cutting grass. Most of the farmers were bitten in rice fields.

More than half the victims were bitten on the foot or toe—through treading on the snake (none wore shoes at the time of the bite). Of the 10 subjects bitten on the leg, eight were bitten in the upper part of the limb, presumably owing to the cobra's habit of rearing up when alarmed. Bites from adult cobras (90 cm. or longer) tended to cause more severe poisoning than bites from young (20–59 cm.) or growing (60–89 cm.) specimens, but there were exceptions to this tendency (see Table I). Although Malayan cobras can "spit" (a process of blowing venom from the fang tips by explosive exhalation), there were no instances of "spitting" at the victims in this series. In Cases 36 and 43 the cobra was yellow (*N. naja kaouthia*), but in the remaining cases it was the usual black subspecies *N. naja leucodira* (see Fig. 1). Use of first-aid measures, particularly tourniquets, made no discernible difference to the severity of subsequent poisoning. None incised the site of the bite though three applied herbs. Thirty-four of the victims reached hospital within three hours of the bite.

Incidence of Poisoning.—In 21 patients no poisoning developed and in a further four there was only slight local swelling lasting a few days. Thus in 25 of the 47 proved cobra-bites, negligible or no envenoming followed. Two patients died. The remaining 20 victims all developed local necrosis, but systemic neurotoxic poisoning occurred in only four of them.

Local Poisoning

Pain, then variable swelling and later necrosis, were the outstanding features of local poisoning. In most cases pain started immediately after the bite. It remained severe for about three days in patients developing slight necrosis (final area under 10 sq. cm.) or moderate necrosis (final area 10–99 sq. cm.); in seven patients with more extensive necrosis (100–600 sq. cm.) severe pain lasted for an average of 10 days (see Table II). Swelling usually started two to three hours after

TABLE I.—*General Features of 47 Cobra-bites*

		Grade of Poisoning			
		Nil	Negligible	Necrosis (No Systemic)	Systemic*
Total No. of patients		21	4	16	6 (2)
Males		14	4	14	3 (1)
Females		7	—	2	3 (1)
Age	0–19 years	7	2	4	2 (1)
	20–49 „	12	1	8	2
	50+ „	2	1	4	2 (1)
Race	Malay	14	1	6	4 (1)
	Chinese	4	3	6	2 (1)
	Indian	3	—	4	—
Bitten in the light		13	4	12	6 (2)
„ „ „ dark		8	—	4	—
Circumstances of bite	Farming	7	—	9	3
	On path	7	1	4	1
	In house compound	4	2	2	2 (2)
	In house	3	1	1	—
Bite site	Toe	5	2	3	—
	Foot	11	—	4	1
	Leg	2	1	3	4 (1)
	Finger	3	1	4	1 (1)
	Hand	—	—	2	—
Snake length (cm.)	20–59	11	1	4	1 (1)
	60–89	7	3	6	1
	90–185	3	—	6	4 (1)
Tourniquet used		10	3	9	5 (2)
„ not used		11	1	7	1
Bite–admission interval (hours)	2 or less	10	1	7	3 (1)
	Over 2 to 3	9	—	3	1 (1)
	„ 3 „ 26	2	3	6	2
No. of fang marks	1	11	1	6	—
	2	9	3	9	5 (1)
	3	1	—	1	1 (1)

* Two fatal cases in parentheses.

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the bite and reached a maximum in 24 to 48 hours. Generally speaking, the amount of swelling and the speed of its development were distinctly less than in the swelling of Malayan-viper-bite poisoning (Reid, Thean, Chan, and Baharom, 1963). Swelling involving the whole limb is not uncommon in viper-bites but is rare in cobra-bites. A constant feature of local swelling from cobra-bites is a dusky discoloration around the bite marks, extending in area and deepening in colour each day. About the third or fourth day the grey-black area becomes encircled by a red raised rim, sometimes studded with small blisters. In about half the cases sanguineous blisters developed over the middle of the dusky area: they were usually small, rarely exceeding 3–5 cm. diameter, but in two cases they involved the whole dorsum of the foot. After four to five days fluctuation was often evident: incision released red-yellow material and revealed necrosis of subcutaneous tissue. The extent of sloughs was invariably much wider than the surface changes suggested (see Figs. 2–4). In Case 38 necrosis was very extensive: yet *no* neurotoxic signs supervened.

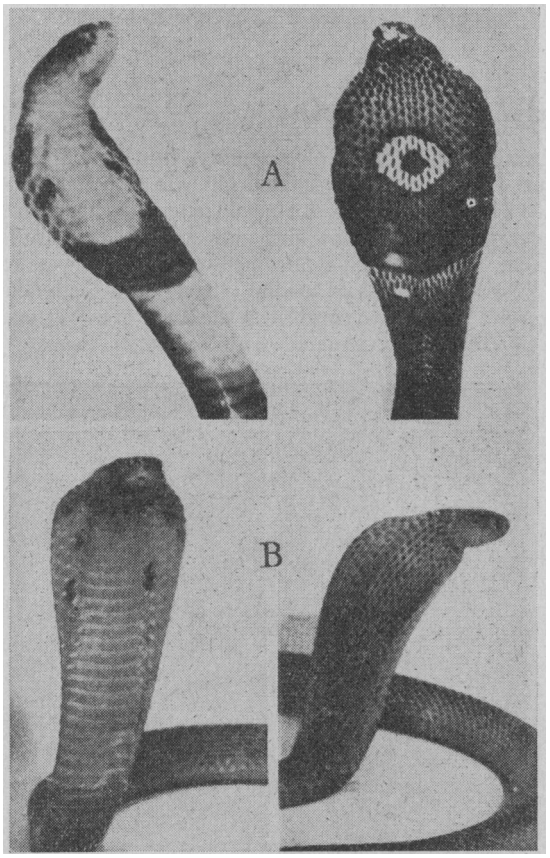

FIG. 1.—In Malaya the common cobra subspecies *N. naja leucodira* (A) is uniform black with blue-grey belly; a black bar and a pair of spots appear on the front of the hood and an oval or diamond-shaped white ring on the back. The yellow cobra *N. naja kaouthia* (B) has no bar across the throat and no ring on the back of the hood.

Case 38.—While cutting grass a 44-year-old Indian was bitten on the right wrist by a cobra 120 cm. long. He applied a ligature just above the wrist and reached hospital two and a half hours after the bite, when the hand and forearm were already much swollen (13 cm.). Within 12 hours of the bite swelling had reached the shoulder (21.5 cm.). From the time of admission I observed him closely for systemic poisoning, particularly in view of the marked swelling. Initially he had a headache, and two days after the bite he was apathetic; blood-pressure dropped from 120/90 on admission to 70/60. Two pints (1,140 ml.) of blood were therefore transfused, and next day the B.P. was 120/80. Electrocardiograms (twice daily during the first week) remained normal. *No* neurotoxic symptoms or signs developed at any time. No antivenom was given, but he received prednisone 40 mg. daily during the first week, the dose being tapered off during the second week. Two weeks after the bite necrosis extended from knuckles to lower arm, an area of 320 sq. cm. (see Fig. 5). Sloughs were excised and skin was grafted. Healing occurred 91 days after the bite.

TABLE II.—*Clinical Details of 20 Cobra-bites with Necrosis (Four with Systemic Poisoning in Addition)*

		Maximum Area of Necrosis (sq. cm.)		
		<10	10–99	100–600
Total No. of patients		10	3	7 (4)*
Pain duration (days):				
Severe pain	Mean duration	3·4	2·5	10·0
	Range	0–17	2–3	1–27
All grades pain	Mean	8·0	14·0	52·0
	Range	1–24	5–33	13–97
No. of patients having	Poor sleep more than 1 night	4	1	4 (2)*
	„ appetite over 1 day	3	1	3 (1)*
	Abdominal pain	2	1	0
	Vomiting	2	1	2 (2)*
	Thirst	2	1	2 (1)*
Maximum limb swelling	No. with 1–5 cm.	6	1	0
	„ „ 6–10 cm.	2	2	1
	„ „ 11–34 cm.	0	0	5 (3)*
	„ not measured	2	0	1 (1)*
Patients given antivenom	Total No.	7	1 (1)†	2
	Mean healing-time (days)	40·0	123	113
	Range (days)	12–65	123	80–146
Patients not given antivenom	Total No.	3 (1)†	2	5 (2)†
	Mean healing-time (days)	37·0	68	94
	Range (days)	14–55	46–90	79–120

* Patients with systemic poisoning as well as necrosis.
† Patients given prednisone.

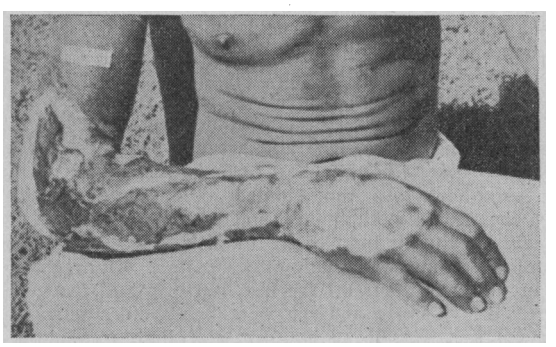

FIG. 5.—Case 38. Despite very extensive necrosis two weeks after the bite no neurotoxic symptoms of poisoning ensued.

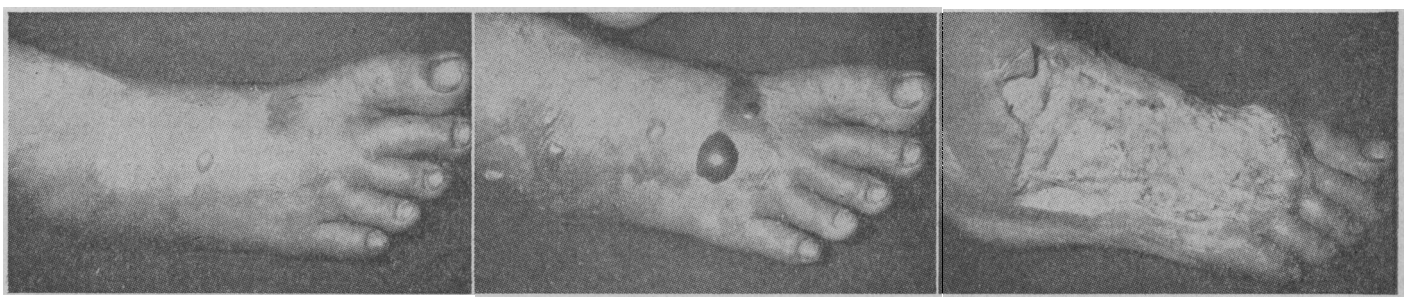

FIG. 2 FIG. 3 FIG. 4

FIG. 2.—Case 24. One day after the victim trod on a 114-cm. cobra in the family grocery shop: he was bitten on the dorsum. FIG. 3.—Case 24. Three days after the bite discoloration was pronounced and blisters had extended. FIG. 4.—Case 24. When sloughs were excised five days after the bite, necrosis was found to involve the whole dorsum. Healing took 123 days. No systemic poisoning developed.

In several instances the local reaction was at first deceptively slight and the patient would have been discharged if experience had not shown that some degree of necrosis almost invariably followed in such cases. Six patients with necrosis (all less than 10 sq. cm., except Case 33 with 72 sq. cm.) remained afebrile. In 14 patients (four with systemic poisoning) fever lasting a few days appeared to be due to serum reactions in four cases, to venom allergy in Case 45, and to bronchitis in Case 29. In the remaining eight patients fever was presumably due to the local necrosis. In Case 43 the patient was febrile for six weeks but in the other seven cases fever lasted only three to five days. Vomiting and abdominal pain rarely occurred, but were divided equally in patients with purely local poisoning and in subjects with systemic poisoning (see Table II).

Systemic Poisoning

The earliest symptom of systemic poisoning was drowsiness, which occurred in all six systemic cases (Nos. 42–47), starting one to five hours after the bite. Difficulty in opening the eyes, speaking, opening the mouth, moving the lips, and swallowing followed three to four hours later ; general weakness was usually the last symptom to develop. In Case 45 ptosis and external ophthalmoplegia lasting three days were the sole neurological deficits—no paresis of neck, trunk, or limb muscles occurred and tendon reflexes remained briskly normal. In Case 44 ptosis and difficulty in lifting the head were followed by depression (one day after the bite) then complete loss of tendon reflexes three days after the bite: but there was *no* objective limb paresis. The most severely poisoned victim who recovered was Case 43.

Case 43

A 70-year-old Malay farmer was bitten on the lower part of his right leg at 9 a.m. by a 92-cm. yellow cobra while planting rice. He applied a cloth ligature and arrived at hospital four hours after the bite ; 50 ml. of Haffkine antivenom with 1 ml. of hyaluronidase was injected intramuscularly. Apart from moderate local pain, he was feeling well. At 2.15 p.m. drowsiness and difficulty in opening his jaws started: the pulse rate was 64, B.P. 120/74. At 6 p.m. he appeared apathetic. Pupils reacted briskly to light. Ptosis was severe—he could not open his eyes even though wrinkling of forehead and eye and facial movements were unimpaired. He was unable to open his mouth or swallow and tongue protrusion was very limited. A general flaccid paresis affected mainly the neck, trunk, and proximal limb muscles. He was unable to lift his head or sit up, although he could turn on to his side: breathing was shallow and mainly diaphragmatic. He could lift all four limbs off the bed, but grip and foot-dorsiflexion were feeble. Tendon reflexes were brisk and plantar responses flexor. There was no pain on passive limb movement and no tenderness on pressing muscles—unlike poisoning by sea-snake-bite (Reid, 1961a). No nystagmus or sensory changes (light touch, vibration, temperature, position sense) were observed. B.P. was 115/70.

A further 100 ml. of Haffkine antivenom in 300 ml. of normal saline was given by intravenous drip between 7.30 and 8.15 p.m. At 9.15 p.m. he felt better ; he could lift his head, open his jaws and protrude his tongue (almost normally), and was breathing more fully. Three days after the bite muscle-power was objectively normal. In contrast, tendon reflexes became progressively depressed and by the third day were absent: but three days later they were normally brisk. During the first week he remained apathetic and the B.P. fell to 80–90/70–40. E.C.G.s (initially normal) showed elevation of ST segments in right chest leads followed by inversion of T waves. Clinical examination revealed nothing of note, heart sounds being normal. Thereafter B.P. remained low and temperature raised (for six weeks), but otherwise from the second week onwards only local poisoning was present. E.C.G.s returned to normal seven days after the bite.

The bitten leg rapidly became swollen from foot to groin (13.5 cm. 24 hours after the bite ; 17.5 cm. 48 hours after the bite). When sloughs were excised two weeks after the bite, necrosis extended from ankle to mid-thigh—an area of 600 sq. cm. (see Fig. 6). One month later skin was grafted: this was partially successful, but a second graft was needed four months after the bite. Healing was complete 146 days after the bite.

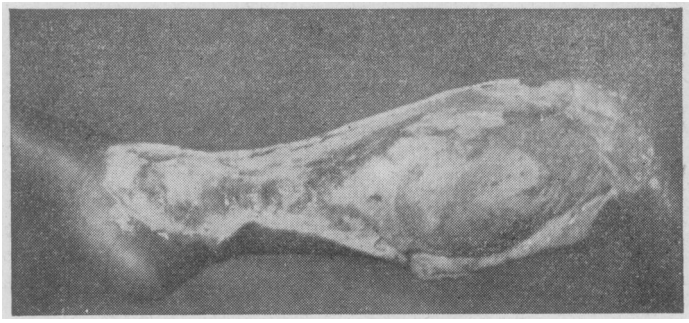

FIG. 6.—Case 43. When sloughs were excised two weeks after the bite necrosis extended from ankle to mid-thigh.

Neurotoxic Features : Course

Neurotoxic features resolve rapidly, usually within a week. In Case 42, a 7-year-old Chinese girl was bitten by an 83-cm. cobra. Drowsiness, ptosis, facial paresis, and difficulty in swallowing ensued. Limb and neck paresis (the latter giving rise to the " broken-neck syndrome "—see Fig. 7) were followed by depression then loss of tendon reflexes, and these neurotoxic features did not resolve completely until two weeks after the bite (exceptionally long compared with the other cases).

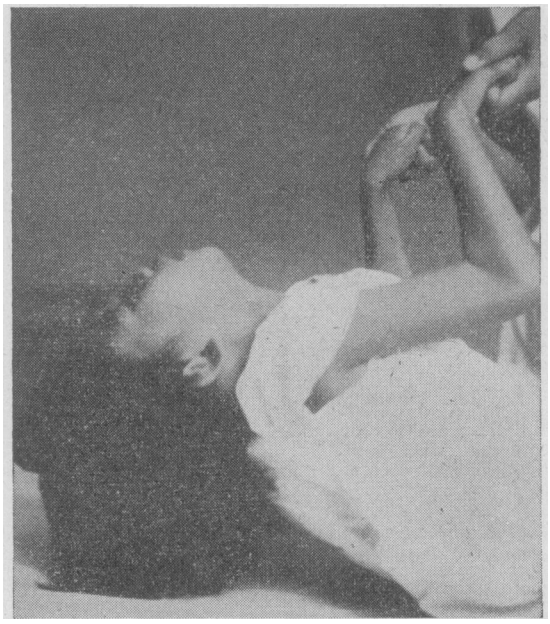

FIG. 7.—Case 42. Neurotoxic paresis of neck muscles resulted in the " broken-neck syndrome ": when the trunk was passively lifted the head lolled back.

Two patients died. One, a 62-year-old Chinese woman (Case 46), was bitten at 5 p.m. on the left ring-finger by a 134-cm. cobra and died eight hours later. At 5.45 p.m. she was given 20 ml. of Haffkine antivenom intramuscularly: her only complaint was severe pain ; B.P. was 245/120, pulse rate 100. At 11 p.m. she became comatose ; B.P. 240/140, pulse rate 142 ; pupils reacted to light and tendon reflexes were brisk. A further 100 ml. of Haffkine antivenom was given by intravenous drip, but she died in two hours. The other, a 5-year-old Malay boy (Case 47), died three and three-quarter hours after the bite (by a 55-cm. cobra). Haffkine antivenom (50 ml.) was

given intramuscularly 30 minutes after the bite. On arrival in the ward he was drowsy and restless but seemed to improve with oxygen. He could move the limbs until shortly before his death. Twitching of the limbs—but no convulsions—occurred. No necropsies were allowed.

Cardiovascular Effects

Generally the pulse rate was slow on admission and later rose, particularly when fever accompanied the local necrosis. B.P. remained normal except in Cases 38 and 43, in the two fatal cases (Cases 46 and 47), and during anaphylactic reactions. Chest radiographs and serial E.C.G.s, including standard and unipolar and eight chest leads (V4R to V6), were normal in all 13 patients with necrosis (the remaining three subjects did not have radiographs or E.C.G.s), and in two of the four patients surviving systemic poisoning. In Case 44 the heart shadow was enlarged because of gross anaemia present before the bite (haemoglobin on admission was 4.7 g./100 ml.). E.C.G.s remained normal. In Case 43 the fall in B.P. and the E.C.G. changes have already been recounted: chest radiographs were normal.

Venom Allergy

In Case 45 urticaria of face and limbs with fever occurred during the first two days after the bite. No antivenom or drugs had been given to cause these. They quickly resolved with prednisone. The patient had not previously been bitten by a snake and admitted no previous or family history suggestive of allergy. Local swelling was moderate (9 cm.) and subsequent necrosis was 108 sq. cm. No enlargement of lymph nodes was observed in this case (or in other cases).

Haematology

In the more severely poisoned subjects the white blood cell count was moderately raised during the first few days. In three systemic cases (Nos. 42, 43, and 45) rise of serum bilirubin to 2–3 mg./100 ml. and excess of urinary urobilinogen during the first few days, followed by a fall in the haemoglobin of 3–4 g./100 ml. and increase of reticulocytes, suggested mild haemolysis. Schumm's test and the direct Coombs test were negative. Tourniquet test, platelets, clotting-time and quality, bleeding-time, and one-stage prothrombin-time were always normal.

Biochemistry

Proteinuria was present for two to four days in all systemic cases, but blood urea remained normal except in Case 45, where it rose to 71 mg./100 ml. by the fifth day and fell to normal by the ninth day. The urine output volume was satisfactory. No abnormal urine pigments (haemoglobin or myoglobin) were detected. Serum electrophoresis showed occasional minor fluctuations with increased globulin. Electrolytes (sodium, potassium, and calcium) remained normal. Serum glutamic oxalo-acetic (S.G.O.T.) and pyruvic transminase (S.G.P.T.) estimations remained normal in four cases of local poisoning (necrotic areas in sq. cm. being 0.25, 1, 96, and 276). This emphasizes that cobra-bite necrosis does not involve skeletal muscle—in contrast to the myotoxic sea-snake envenoming, which is reflected by a very high S.G.O.T. (Reid, 1962). Enzymes were estimated in only one systemic case (No. 45), in which there was a mild rise of S.G.P.T. (probably due to the allergic reaction) lasting two weeks; S.G.O.T. rose slightly during the first 10 days.

Bacteriology

In four cases cultures were taken from blister-fluid aspirates and from sloughs at the time of excision. In one case *Staphylococcus aureus* was cultured; in the other three cases *Proteus* or *Alcaligenes faecalis* grew.

Progress and Effect of Treatment

Even with minor necrosis (less than 10 sq. cm.) healing-time averaged nearly six weeks. With moderate necrosis it averaged 12 weeks and in the seven cases with severe necrosis (100 sq. cm. or more) the mean healing-time was 15 weeks (see Table II). Half of the 20 patients with necrosis (including two of the four subjects surviving systemic poisoning) received antivenom usually 50 ml. intravenously (dose range was 20–150 ml.). In four cases the antivenom was monospecific anti-*N naja* horse serum from the Queen Saovabha Memorial Institute, Bangkok; in six cases the antivenom was polyspecific horse antiserum made at the Haffkine Institute, India, from venom of *N. naja, Bungarus coeruleus, Vipera russelli,* and *Echis carinatus*. Both antivenoms neutralize about 6 mg. of *Naja naja* venom per 10-ml. phial as tested by *in vitro* mixing and subsequent injection into small animals. Neither antivenom appeared to prevent or ameliorate local necrosis. In systemic poisoning improvement followed (especially in Case 43), but it was not dramatic. Three of the four patients receiving Bangkok antivenom—which is "raw" antiserum—developed both immediate (one severe, two moderate), and delayed (all moderate) serum reactions. Only one of the six subjects given Haffkine antivenom had a reaction—a moderately severe immediate one; no late reaction developed. Haffkine antivenom was concentrated by the ammonium sulphate method. Tetanus antiserum was given to 6 of the 20 patients developing necrosis: one subject had a moderate delayed reaction (no antivenom was given in this case).

In four cases prednisone was given, including Case 45, in which the patient had systemic poisoning and venom allergy. The dose was 40 mg. daily for the first week, then tapered off over one to two weeks. In Case 45 it seemed to delay the appearance of necrosis without affecting the final severity. In other cases no discernible benefit ensued. Nine of the 20 patients had sloughs excised under a general anaesthetic and skin-grafting was applied in four severe cases. In two patients it appeared to shorten the healing-time considerably, but in the other two (Cases 24 and 43) the grafts were only partially successful. Local applications included normal saline, petroleum-jelly gauze, eusol, scarlet-red ointment, penicillin cream, neomycin cream, and plaster-of-Paris. Probably normal saline was as effective as the other applications. Five of the 20 patients with necrosis received no systemic antibiotics; in all five, necrosis was less than 10 sq. cm. Five received only penicillin (three with necrosis less than 10 sq. cm.). Seven received penicillin with streptomycin and later tetracycline (all had necrosis exceeding 70 sq. cm.), and three subjects had tetracycline alone. Thus it is evident that the more severe the necrosis the more likely would a variety of antibiotics be used: the general impression was that, no matter how soon they were given, they made little contribution to recovery.

Discussion

The minimum lethal dose of Malayan-cobra venom injected subcutaneously in dogs is 0.6 mg. of dried venom per kg. Assuming humans are equally susceptible, a lethal dose for an adult 70-kg man would be 42 mg. During recent years the average venom yield at the Snake and Venom Research Institute, Penang, from common cobras is 90 mg., the maximum being 394 mg.—sufficient to kill at least nine men. Thus the low morbidity and mortality—in more than half the bites negligible

or no poisoning followed—is quite remarkable and requires repeated emphasis. It is most important for clinicians to realize that such a larger proportion of victims escape with little or no envenoming. In some cases, when the cobra was milked shortly after biting these victims, enough venom was obtained to have killed several adult men. Bites of human victims by poisonous snakes are defensive reactions in which it is fortunately unusual for much venom to be injected.

The outstanding feature of poisoning is local necrosis, which may be very extensive. Few doctors are aware of this predominant effect in human victims—probably because their impressions are based on the neurotoxic effects in small animals. Cobra venom is either rapidly fatal to such animals from neurotoxic and cardiac effects or, if recovery ensues, no local effects have been observed. Yet local necrosis is well documented in Indian cobra bites. Cookson (1867) wrote: "If the patient survives the shock of a cobra's poison . . . extensive sloughing and suppuration will make recovery very doubtful and when it does occur the sufferer will often remain a sad cripple." Richards (1882) and Harty (1926) record brief neurotoxic symptoms followed by local necrosis. Michael (1922) recorded severe neurotoxic effects and thought the victim (seen seven and a half hours after the bite in his village) would die. But the relatives had not given up hope, because the cobra was still alive. "Six days later, to my great surprise and delight, he walked into the hospital displaying a very gangrenous hand and arm but otherwise well." Necrosis without any neurotoxic symptoms has been reported by Moore (1868), Bull (1880), Roy (1882), Gaudoin (1907), Reid (1901), Macgregor (1906), and Hennessy (1918). Curiously, none of these authors comment on the local necrosis, which was extensive in several cases.

Other papers from India (Cornish, 1880; Rigby, 1887; Cadge and Pratt, 1892; Prall, 1894; Rogers, 1905; Khisty, 1915; Hazra, 1921; Gharpurey, 1932) report cobra-bites, but either no poisoning followed or recovery was presumed in a few days and no follow-up was recorded. Similarly, Benyajati *et al.* (1961) reported six cases of cobra-bites in Thailand. These patients were discharged one to three days after the bite, so that local necrosis may well have been overlooked. Necrosis without neurotoxic effects has occurred from the bite of a Hong Kong cobra (J. S. Romer, personal communication, 1958). That necrosis following cobra-bites in India is not confined to human victims is confirmed by Fayrer's (1870) report of a krait, *Bungarus fasciatus*, being bitten by a cobra. Five days later the bite site "ulcerated and a putrid opening in the tissues exposed the ribs." I have been unable to find any clinical accounts published of African-cobra bites. Personal communications from South Africa (P. A. Christenson, 1963, and T. Brondum, 1963) and Nigeria (H. H. Gray, 1963), confirm the lack of clinical information: necrosis following snake-bite in human victims is not uncommon, but the snake has not been identified as a cobra.

Is the necrosis due to bacterial infection introduced at the time of the bite? Several authors write of heavy contamination of the mouths of snakes. Mouth infection of snakes in captivity is undoubtedly a common trouble, but freshly caught snakes do not have a heavy bacterial flora: 30% are sterile (Williams *et al.*, 1934). In my opinion, the fact that over half the victims in this series had distinct fang marks and sometimes teeth marks and yet developed *no* local reaction, excludes the likelihood of bacterial infection being important as a primary factor in necrosis. Severe necrosis has resulted in dogs from subcutaneous injection of sterile Malayan-cobra venom. I ascribe it to a direct cytolytic effect of the venom. Bacterial infection may follow, but in my opinion this is not usually introduced with the bite.

Systemic Effects

The systemic effects of cobra venom have been extensively investigated in animal experiments for over 100 years. A myoneural curare-like effect (Lauder *et al.*, 1873; Lee *et al.*, 1960) has been observed and direct muscle action (Kellaway and Holden, 1932; Sarkar and Maitre, 1950) has also been invoked in the respiratory failure. Cardiovascular effects are equally pronounced (Feldberg and Kellaway, 1937; Bhanganada and Perry, 1963). Haemolytic effects have been shown by Cunningham (1898), De (1941), and other workers. Clinical evidence of these features—neurotoxic, cardiotoxic, and mild haemolytic effects—was evident in the few patients with systemic poisoning. No effect on blood coagulation was observed.

In 14 fatal cases of cobra-bite received in north-west Malaya during 1955–61 the average death time was 12.6 hours (range 1¼ to 60 hours). Excluding three cases in which death times were unusually long (29, 36, and 60 hours), the average death time was only 4.6 hours (range 1¼ to 8½ hours). This contrasts with average death times of 29.6 hours in 48 cases of sea-snake-bite (Reid, 1961b) and 64.6 hours in 23 cases of Malayan-viper bite (Reid, Thean, Chan, and Baharom, 1963). The relatively rapid deaths in poisoning by cobra-bite are probably due to the smaller molecules of the venom allowing more speedy absorption directly through the blood-stream (Barnes and Trueta, 1941). But the mode of death remains obscure. Thus limb movements may be continued until shortly before death in both human victims and dogs—the paresis does not always appear to be sufficiently great to be fatal. In dogs, a constant early feature following lethal or near-lethal Malayan-cobra-venom injection is production of abundant frothy sputum suggesting pulmonary oedema. In Case 43, the most severely poisoned victim who recovered, the effects appeared to be more cardiotoxic than neurotoxic or haemolytic.

In the four patients given prednisone in this series no benefit was observed. Similarly, in a controlled therapeutic trial in poisoning by Malayan-viper bite (Reid, Thean, and Martin, 1963b) prednisone brought no benefit in either local or systemic envenoming. I have observed fatal tetanus (to be published) following viper-bite necrosis and therefore think the use of tetanus antiserum may be justified in the minority of cobra-bite victims developing necrosis—after necrosis is clinically evident. Early excision of sloughs is important, but it should be emphasized that necrosis is usually confined to subcutaneous tissues: tendons and muscles are rarely involved, although muscles may appear necrotic. Such muscles might be excised by an over-enthusiastic or inexperienced surgeon. I have seen this happen with disastrous local results, the wound taking much longer to heal than if the muscle had been left alone, and permanent limb disablement following. Generally speaking, normal saline is the best local dressing. Systemic antibiotics may sometimes be helpful and skin-grafting should be carried out early, even if infection is still evident, rather than late. Blood transfusion improves the general condition of toxic patients and is particularly necessary when the victim is anaemic before being bitten. In very severe cases, with respiratory failure established on arrival at hospital, tracheostomy (Campbell and Young, 1961) with or without intermittent-positive-pressure artificial respiration (Richards, 1873) might conceivably prolong survival and enable large amounts of cobra antivenom to be used to save the victim.

Specific antivenom is the most important therapeutic agent. That it is ineffective in combating local necrosis is not surprising. In Malayan-viper-bite poisoning, specific antivenom does not prevent or ameliorate local effects, including necrosis, but is most effective against systemic poisoning (Reid, Thean, and Martin, 1963b). Cobra-bites are not common enough in Malaya (Reid, Thean, and Martin, 1963a) to permit a similar controlled therapeutic trial. From the present series I have formed a definite clinical impression that specific antiserum *is* effective in combating systemic envenoming but that the effects are not as dramatic as those of specific antivenom in sea-snake-bite (Reid, 1962) or Malayan-viper-bite poisoning. Dosage of antivenom is, however, a major problem. Recent research in

dogs has shown that specific Bangkok antivenom, injected intravenously one hour after subcutaneous administration of venom, neutralizes only 4 mg. of dried Malayan-cobra venom per 10-ml. ampoule, while one polyspecific Haffkine 10-ml. ampoule neutralizes 6 mg.

The maximum dosage in this series was 150 ml. of Haffkine antivenom (in Case 43). This would neutralize about 90 mg. of cobra venom, and the victim (weighing 41 kg.) might resist of his own accord 0.5 mg./kg., or 20 mg. of venom. But the single bite of an adult cobra can inject much more than the equivalent of 110 mg. of dried venom. In a severe case of systemic poisoning at least 20 ampoules of specific antivenom should be given. Lamb (1904) maintained that when estimating the amount of antivenom needed for Indian-cobra bite, one should have in mind a dose of 250–350 mg. of venom. Acton and Knowles (1921) suggested 100 to 400 ml. of antivenom intravenously—100 ml. to be given initially, and, if symptoms progress, a further 100 ml., and so on until the maximum dose of antiserum is reached. I think 100 ml. should be repeated every one to two hours if distinct clinical improvement does not occur. In view of the rapid absorption of cobra venom, intravenous-drip technique is mandatory, with the usual precautions against serum reactions. The indication for giving antivenom is clinically evident systemic poisoning as shown by objective paresis (especially ptosis) and apathy with or without hypotension.

It must, however, be emphasized again that few snake-bite victims—less than a fifth—require antivenom. Absence of local swelling is a most valuable clinical indication that no venom has been injected in Asian-cobra and Asian-viper bites. St. Paul, after being shipwrecked on the island of Melita, was bitten by a viper. "And when the barbarians saw the *venomous* beast hang on his hand, they said among themselves, No doubt this man is a murderer, whom, though he hath escaped the sea, yet vengeance suffereth not to live. And he shook off the beast into the fire, and felt no harm. Howbeit they looked when he should have swollen, or fallen down dead suddenly: but after they had looked a great while, and saw no harm come to him, they changed their minds, and said that he was a god" (Acts, xxviii, 4–6).

Summary

The clinical features following 47 proved cobra bites received in north-west Malaysia are summarized. More than half the patients had negligible or no poisoning—a most important prognostic and therapeutic fact. Absence of local swelling one hour or more after the bite is a valuable clinical indication that no venom has been injected.

Neurotoxic effects in human subjects are rare, occurring in only 6 (13%) of the 47 victims. The most common feature of poisoning is local necrosis, which can be very extensive without any systemic envenoming.

Specific antivenom does not prevent or ameliorate local necrosis. Specific antivenom should be given only after systemic poisoning becomes clinically evident as shown by objective paresis and apathy, with or without hypotension. The *minimum* effective antivenom dose is 100 ml. and the intravenous route is mandatory.

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